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POSTER ABSTRACTS

605.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: LYMPHOID NEOPLASMS

Population Pharmacokinetics and CD20 Binding Dynamics for Mosunetuzumab in Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma (R/R NHL)

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Introduction: Mosunetuzumab (Mosun) is a CD20xCD3 T-cell engaging bispecific antibody that redirects T cells to eliminate malignant B cells. Clinical data from GO29781 (NCT02500407), a Phase I/II, open-label, multicenter dose-escalation and expansion study of Mosun in pts with relapsed or refractory (R/R) non-Hodgkin lymphoma (NHL), was used to develop a population pharmacokinetic (popPK) model describing Mosun concentration-time data. Prior to initiation of Mosun, many patients had circulating levels of other anti-CD20 drugs (e.g. rituximab (R) or obinutuzumab (G)) from prior treatment. In order to elucidate exposure-response (ER) relationships in the presence of these competitors, CD20 binding and R/G pharmacokinetics were incorporated into the popPK model to calculate the Mosun CD20 receptor occupancy percentage (RO%) over time.
Methods: Mosun PK data were available in 439 pts with indolent or aggressive R/R NHL who received either Mosun fixed dosing (n= 32; 0.05-2.8mg every 3 weeks (q3w)) or Cycle 1 step-up dosing (n=407, 0.4/1.0/2.8 - 1/2/60/30mg). The popPK model was developed using NONMEM® software (v7.4.3), with a clinical cut-off date of December 4, 2020. Clinically relevant covariates were investigated for their potential to explain Mosun PK variability. The Mosun CD20 RO% time course for each pt was derived by integrating the Mosun, R, and G model predicted concentration-time courses and their respective CD20 affinities (Kds) into the popPK model. R and G concentration-time courses were predicted by the model using their baseline values and published half-lives, and binding kinetics were assumed to be at equilibrium.
PopPK model simulations (n=1000) were done with the final model to establish Mosun concentration ranges for the approved 1/2/60/30 mg dose regimen, given that this regimen was designed to mitigate cytokine release syndrome (CRS) through its step-up Cycle 1 design. Additional popPK model simulations, incorporating Mosun dose delays, were conducted and compared to the 1/2/60/30 mg nominal dose regimen to inform treatment resumption protocols necessary to mitigate CRS.
Results : A two-compartment PK model with time-dependent clearance (CL) best described Mosun PK. Mosun CL decreased from an initial value of 1.08 L/day transitioning to a steady state clearance of 0.584 L/day by Cycle 4 (Figure 1A). Mosun terminal phase half-life at steady state was 16.1 days. Concentrations of R/G were present in 50% of patients prior to Mosun therapy (Figure 1A), and the median predose R/G concentration for these patients was 10.0 μg/mL. Statistically relevant covariates on PK parameters included body weight, albumin, sex, tumor burden, and baseline concentrations of R/G; however, no covariate was deemed to have a clinically relevant impact on PK at the recommended dose of 1/2/60/30mg.
Mosun CD20 RO% was more variable than Mosun PK (Figure 1B), attributed to the large variability in baseline R/G concentrations. The 60mg loading doses increased Mosun CD20 RO% to steady-state ranges by Cycle 1 (Figure 1B), thereby providing Mosun efficacious exposure in the presence of competing residual, transient R/G concentrations from prior treatment therapies (Figure 1A).
From the popPK model simulations, patients with dose delays greater than or equal to 6 weeks had Mosun concentrations that fell below levels after the Day 1 (1mg) and Day 8 (2mg) doses; as such, these pts are instructed to repeat these doses prior to treatment continuation. For Mosun dose delays less than 6 weeks, popPK simulations supported pts either to repeat the last Mosun dose administered, or to continue along with the planned regimen [Lunsumio ® USPI].
Conclusions: Mosun PK was characterized using a two-compartment model with time dependent CL. R/G PK and CD20 binding kinetics were incorporated into the Mosun popPK model to calculate Mosun CD20 RO% over time. The use of two 60mg loading doses enables early achievement of Mosun steady-state target CD20 RO% range, especially benefitting those

pts with high levels of precirculating R or G. Simulations with the popPK model supported labeling recommendations for restarting Mosun treatment after dose delays.

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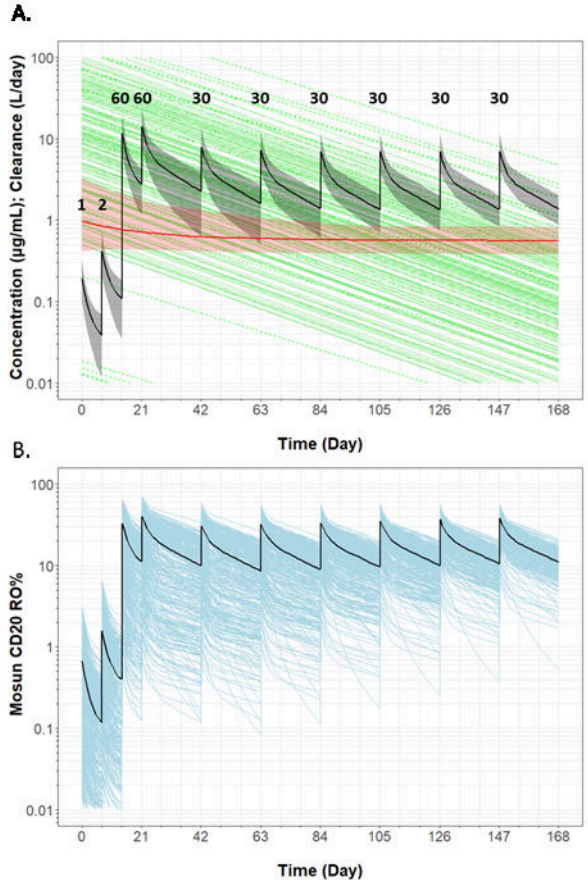
Disclosures Bender: *F. Hoffmann-La Roche Ltd / Genentech, Inc.:* Current Employment, Current equity holder in publicly-traded company. **Li:** *F. Hoffmann-La Roche Ltd / Genentech, Inc.:* Current Employment, Current equity holder in publicly-traded company. **Marchand:** *F. Hoffmann-La Roche Ltd / Genentech, Inc.:* Consultancy. **Turner:** *F. Hoffmann-La Roche Ltd / Genentech, Inc.:* Current Employment, Current equity holder in publicly-traded company. **Li:** *F. Hoffmann-La Roche Ltd / Genentech, Inc.:* Current Employment, Current equity holder in publicly-traded company. **Vadhavkar:** *F. Hoffmann-La Roche Ltd / Genentech, Inc.:* Current Employment, Current equity holder in publicly-traded company. **Wang:** *F. Hoffmann-La Roche Ltd / Genentech, Inc.:* Current Employment, Current equity holder in publicly-traded company. **Deng:** *F. Hoffmann-La Roche Ltd / Genentech, Inc.:* Consultancy. **Lu:** *F. Hoffmann-La Roche Ltd / Genentech, Inc.:* Current Employment, Current equity holder in publicly-traded company. **Jin:** *F. Hoffmann-La Roche Ltd / Genentech, Inc.:* Current Employment, Current equity holder in publicly-traded company. **Li:** *F. Hoffmann-La Roche Ltd / Genentech, Inc.:* Current Employment, Current equity holder in publicly-traded company. **Yin:** *F. Hoffmann-La Roche Ltd / Genentech, Inc.:* Current Employment, Current equity holder in publicly-traded company, Patents & Royalties. **Wei:** *F. Hoffmann-La Roche Ltd:* Patents & Royalties; *Genentech, Inc.:* Current Employment; *F. Hoffmann-La Roche Ltd:* Current equity holder in publicly-traded company. **Chanu:** *F. Hoffmann-La Roche Ltd / Genentech, Inc.:* Current Employment, Current equity holder in publicly-traded company.

Figure: PopPK Model–Predicted Time Courses for: (A) Mosun, R, and G and (B) Mosun CD20 Receptor Occupancy % in GO29781



Within panel A are simulated pt popPK model–predicted profiles (n=439) for the 1/2/60/30 mg dose regimen (doses labeled in bold); simulations are based on individual pt PK parameter estimates and use nominal dose times and dose amounts. The black line (median) and shaded grey region (95th prediction interval) represent the Mosun concentration–time profiles (µg/mL). The solid and dashed green lines are the individual predictions for pt's residual R (n=195) or G (n=35) concentration–time profiles (µg/mL), respectively, from prior treatment therapies. The red line (median) and shaded red region (95th prediction interval) represent the pt clearance (CL)–time courses (L/day). Within panel B are the corresponding individual Mosun CD20 RO%–time profiles for each pt in panel A. The black line (median) and blue lines represent the Mosun CD20 RO% for these pts.

CL, clearance; G, obinutuzumab; Mosun, mosunetuzumab; PK, pharmacokinetic; popPK, population pharmacokinetic; pt, patient; R, rituximab; RO%, receptor occupancy percentage

Figure 1

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